ENZYME MOBILIZATION BY MEANS OF ROENTGENRAY STIMULATION.

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It is at present a recognized principle in the therapeutic application of photodynamic and radiant agents, including roentgen rays, radium, Finsen and red rays, sunlight, etc., that, apart from the direct effect on the exposed tissue, these agents may bring about a distinct systemic alteration.

Clinically this alteration is made evident in two ways: There is first of all the recognition that the effects of radiant agents may be exerted on remote pathological lesions. Thus lupus and other tuberculous processes may be benefited by light rays acting on remote body surfaces. Secondly, we recognize a general intoxication, a phenomenon of varying intensity, ranging from mere transitory and subjective symptoms to an actual fatal intoxication. To these latter forms the term roentgenray anaphylaxis has not infrequently been applied, but, of course, improperly. The general intoxication is frequently elicited when large lymphatic structures, abdominal viscera or cell-rich neoplasms or inflammatory exudates are exposed for any length of time. Walsh[1] is said to have been one of the first observers to record such toxic effects.

The mechanism of this reaction, apart from the assumption that it is due to the reabsorption of the products of cell destruction, has not been clearly defined. It is known that the intracellular enzymes are influenced by the agents under consideration, and experiments to study the effects upon ferments *in vitro* have demonstrated the destructive effect of radiant energy upon them, the diastasic ferment being the only one that displays considerable resistance to prolonged exposure.

Short exposures, on the other hand, may accelerate enzyme action *in vitro*, according to Richards.[2]

If the possibility exists that by means of irradiation the intracellular enzymes may be altered and their entrance into the blood and lymph current accelerated or retarded, it might seem a plausible method of approach to the problem of altering and controlling the amount and character of the serum ferments and the resultant effect on such local pathological processes as pneumonia[3] and tuberculosis.[4]

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[1] British Med. Jour., 1897, **2**, 272.

[2] Am. Jour. Physiol., 1914, **35**, 224.

We cannot introduce foreign ferments directly into the circulation because of the impossibility of freeing them from more or less toxic admixtures; the advocacy of trypsin injections by Beard,[5] it will be recalled, was along this line but led invariably to a toxic reaction. The intestinal absorption of enzymes is likewise uncertain. The ferment-rich abdominal organs might, however, lend themselves to stimulation by means of the agents under consideration, and, as a result of varying degrees of insult, discharge ferments into the circulation in different amounts. Whipple[6] has noted that liver injury, for instance, causes an increase in the serolipase, and Musser and Edsall,[7] in studying the effect of roentgen rays on the metabolism of leukemic patients surmised that an acceleration of the proteolytic activity resulted from the roentgenray treatment. It may be permissible to quote at length from their interesting paper: "The facts that have just been mentioned demonstrated, we think, that the effect (of the roentgenrays) is not a direct one but one that requires response on the part of the individual. . . . To be more specific concerning the processes that are stimulated and accelerated by the roentgen rays, we consider that it is highly probable that the action is chiefly on autolysis. A considerable number of physiological and pathologic processes have, with considerable probability, been shown to be due to autolysis, that is, to activities that have the characteristics of ferment-like processes and that produce in their course the same classes of substances as those found in the various stages of digestion. The view is now widely accepted that the exudate in pneumonia undergoes resolution as a result of sudden autodigestion, carried out not through bacterial influences but through the activities of the tissues. . . . Following the general trend of the thought, and the direction in which the results of recent experimental work pretty generally point, the most natural explanation of the increase in tissue destruction, when this destruction is dependent upon individual body reaction, is that it is due to acceleration of autodigestive or autolytic processes. The remarkable suddenness and intensity with which the action of the roentgen rays begins immediately after exposure is more direct evidence in favor of the view that autolysis is influenced."

In a second contribution (Edsall and Pemberton[8]) the effect of roentgen rays on unresolved pneumonia was studied as well as

[3] Jobling, J. W., Petersen, W. F., and Eggstein, A. A.: Jour. Exp. Med., 1915, **22**, 568.

[4] Petersen, W. F.: Arch. Int. Med., 1918, **21**, 14.

[5] Enzyme Treatment of Cancer, London, 1911.

[6] Bull. Johns Hopkins Hosp., 1913, **24**, 357.

[7] Tr. Assn. Am. Phys., 1905, **20**, 294.

[8] AM. JOUR. MED. SCI., 1907, pp. 133, 286 and 426. Tr. Assn. Am. Phys., 1906, **21**, 618.

attention directed to possible toxic results that might be related to the effects of the roentgen rays. In these two papers the very definite foundation for the therapeutic application of the rays in stimulation enzyme activity, thereby influencing pathologic processes, was formulated.

Since these papers of Edsall were published a considerable amount of evidence has been accumulating that tends to confirm the view that apart from the antibacterial mechanism involved in recovery from pneumonia a second mechanism, the inception of an active autolysis, plays a considerable role in the crisis (Jobling, Petersen and Eggstein,[9] Lord,[10] Weiss,[11] Blake and Cecil,[12] Petersen and Short,[13] Thomas and Parker,[14] etc.).

In the meantime there has developed, first quite empirically, the so-called non-specific method of treatment of a number of diseases whereby disease processes are either abruptly terminated or markedly influenced by the intravenous injection of a great number of different agents ranging from chemicals—salts, formalin, etc.—through the metallic colloids—silver, arsenic, etc.—to various biological substances—vaccines, milk, protein split products, etc. The intensive study which interest in this field has stimulated, has led to the recognition that the broad basis of this form of therapy rests on common systemic alterations produced by these various substances. Weichardt[15] uses the general term "plasma-activation" to cover the whole series of alterations inaugurated by the non-specific injections. Among these the alteration in the permeability of the cells is perhaps fundamental. The serum enzymes, too, have been found altered, particularly the proteolytic enzymes are seemingly increased in amount. Lindig,[16] Luithlen[17] and others regard this mobilization as of particular significance. Sachs,[18] in his recent review, seems to be of the same opinion.

Considering the fact that the enzyme mechanism very probably plays a role in such pathological conditions as pneumonia and tuberculous infection, and that even in the non-specific reaction the effect of enzyme mobilization is supposed to be of some importance, we thought it might be of interest to study whether by means of the roentgen ray or other similar agents we could bring about the "shedding" of organ enzymes. Studies heretofore reported, such as those of Hall and Whipple,[19] are concerned chiefly with the cause of the roentgen ray shock when large doses are used, while Denis, Martin and Aldrich[20] endeavored to elucidate the same point

[9] Exp. Med., 1915, **22**, 568.

[10] Jour. Am. Med. Assn., 1919, **73**, 1420.

[11] Arch. Int. Med., 1919, **23**, 395.

[12] Jour. Exp. Med., 1920, **31**, 445.

[13] Jour. Infect. Dis., 1918, **22**, 147.

[14] Arch. Int. Med., 1920, **26**, 125.

[15] München. med. Wchnschr., 1918, **65**, 581.

[16] Ibid., 1919, **66**, No. 33.

[17] Wien. klin. Wchnschr., 1913, **26**, 653.

[18] Therap. Halbmonatschr., 1920, **34**, 379.

[19] Am. Jour. Med. Sci., 1919, **157**, 453.

[20] Ibid., 1920, **160**, 555.

by means of massive regional doses in rabbits. Pfeiffer,[21] on the other hand, has already demonstrated that in photodynamic intoxication (he used "rose bengale") a mobilization of serum peptidase takes place.

Apart from the mobilization of enzymes the selective stimulation of organs by means of the roentgen ray or related agents is a related field in which therapeutic applications have been reported only in very recent papers. These include the alteration in the coagulation mechanism following raying of the spleen (Stephan[22]) and the effort to increase the function of certain of the glands of internal secretion by means of stimulating doses.

Experimental. Preliminary experiments were carried out to determine whether variation in enzyme titers occurred in the serum following roentgen ray exposure of the liver, intestinal and splenic area.

Liver Exposure. Dog of 14 kilo. Diet, June 13 to 29, 1917, as follows:

Protein (lean meat)	220 gm.
Carbohydrate (cracker meal)	60 "
Fat (lard)	40 "
Bone ash	35 "
Water	300 "

From June 29 to the termination of the experiment the daily ration was altered so that the animal received 100 gm. of carbohydrate and 25 gm. of fat per day. The normal metabolism of this diet was first studied for a period of several days.

On June 20 (10 A.M.) the liver area was rayed for fifteen minutes (Coolidge tube, 10-inch distance, 8 ma. and 5-inch back spark; no screen). On June 25 the liver was exposed for thirty minutes (8-inch spark) and on June 29 for one hour. (In raying the liver area, parts of the gastro-intestinal tract, pancreas, etc., were, of course, not to be excluded). After a period of four days a superficial burn followed over the area exposed. The animal was killed on July 5. No gross or microscopic alterations were to be found in the abdominal viscera.

It was observed that:

(*a*) The weight of the animal decreased after the second exposure. (about 1000 gm.)

(*b*) That the nitrogen excretion also increased after this exposure. The serum studies revealed the following changes:

(*c*) Exposure was followed by a transient decrease in the non-coagulable nitrogen of the serum with an increase in the amount later. From the original of about 40 mg. per 100 cc the non-coagulable nitrogen increased to 55 mg. at the end of the experiment.

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[21] Ztschr. f. Immunitätsforsch., orig., 1915, **23**, 597.

[22] München. med. Wchnschr., 1920, **67**, 309.

(*d*) A marked mobilization of the protease followed the short exposure and there was no change following the two longer periods of exposure to the rays.

(*e*) The ereptase (peptidase) was increased after the short exposure but immediately decreased after the longer periods.

(*f*) The lipase (esterase) titer increased after the first two exposures but decreased after the longer period.

(*g*) The antiferment titer was quite irregular but gave evidence of a distinct increase after the final exposure.

(*h*) The diastatic activity fluctuated to a considerable extent, but, was as a rule, augmented after the roentgenray exposure.

It was apparent from the experiment that as a result of the roentgen-ray exposure the serum ferments were not only altered quantitatively, but that decided differences in reaction were obtained with different degrees of exposure and consequent stimulation of the liver parenchyma.

Intestinal Exposure. In the following experiment a dog of 19½ kilos was used. The diet was as follows:

Protein	330 gm.
Carbohydrate	130 "
Fat	35 "
Bone ash	40 "
Water	400 "

Because of the rejection of about 375 gm. of the diet on the two-day period following the second exposure the diet was reduced on July 24 to:

Protein	200 gm.
Carbohydrates	100 "
Fat	20 "
Saline	20 "

The water ration was increased to 600, later to 2000 cc per day.

The animal was rayed for periods of time similar to the first, but in this case the upper abdominal viscera were protected so that only the lower intestinal area was exposed. (Distance, 10 inches; 8 ma.; 6-inch spark; no screen).

(*a*) The weight of the animal decreased after the second exposure. This decrease, not associated with a corresponding increase of nitrogen excretion, was probably due to a loss of water content of the animal. The serum alterations revealed the following:

(*b*) A distinct transient increase in the non-coagulable nitrogen after the periods of exposure. There was no permanent alteration of the original amount (25 mg. per 100 cc).

(*c*) Only a slight and transient increase in the protease following the original exposure; no increase after the longer periods of raying.

(*d*) A considerable augmentation of peptidase, reaching the maximum after the second exposure; a decrease after the longest exposure.

(*e*) A lipase curve similar to that following the liver exposure.

(*f*) Marked fluctuations in the antiferment titer, with less evidence of reaction following the final exposure than in the case of the liver.

(*g*) A sharp increase in the diastase after the first two exposures; no change following the longest period.

On the basis of these preliminary experiments we have made a more detailed study of the serum changes following roentgenray exposure of the liver and intestinal and splenic areas in dogs. They were rayed for the following periods: five minutes, ten minutes and twenty minutes with Coolidge tube screened by a 3-mm. aluminum screen, 10-inch distance; 8 ma.; 5-inch backspark and a final unscreened exposure of twenty minutes. The time interval between the exposures varied from five to fourteen days. The exposures were made in the morning, serum samples being obtained before, one-half, five, twenty-four, forty-eight and seventy-two hours after the exposure. The samples were always taken before the animals had been fed.

The following observations were made:

Temperature.
Leukocyte count—differential.
Coagulation time—capillary tube method.
Urine: Volume. Total nitrogen excretion.
Serum enzymes: Protease.
Ereptase (peptidase).
Lipase.
Diastase.
Complement titer.
Antitrypsin titer.

Temperature Changes. The temperature of dogs is, of course, irregular, but we have made observations of the rectal temperature of animals in whom the liver, spleen and intestinal region were rayed.

With moderate dosage (five and ten minutes) little effect was observed, as will be apparent in the following records:

	Before raying.	30 minutes after.	1 hour after.	5 hours after.	24 hours after.
LIVER:					
Dog No. 10	102.0° F.	103.8° F.	102.4° F.	103.0° F.	104.6° F.
Dog No. 13	102.4° F.	102.4° F.	102.4° F.	102.8° F.	101.4° F.
SPLEEN:					
Dog No. 12	103.0° F.	103.4° F.	102.4° F.	102.6° F.	101.8° F.
INTESTINE:					
Dog No. 11	101.4° F.	102.8° F.	102.0° F.	101.8° F.	101.8° F.

When the longer dosage (twenty minutes, with or without screen) was given the temperature changes were of greater amplitude and consistency.

SPLEEN:					
Dog No. 8	101.4° F.	102.2° F.	103.6° F.	104.2° F.	102.0° F.

There was no apparent difference in the degree of reaction whether the splenic, intestinal or liver region was rayed.

The Leukocyte Count. The leukocytic reaction showed considerable differences with the different regions stimulated. In the following tabulation the normal count taken before the roentgen-ray exposure is contrasted with the average of the counts obtained for the half-hour, one-hour, five-hour, twenty-four-hour, forty-eight-hour and seventy-two-hour periods:

	Liver.	Spleen.	Intestine.
Normal	4,000	10,000	3,000
After five hours exposure	7,600	16,700	3.400
Before	3.200	14.200	3,000
After ten minutes exposure	5.600	13.400	8.200
Before	3.400	11.400	7.400
After twenty minutes exposure	10.000	11.300	12.900
Before	4.800	13.700	14.300
After twenty minutes exposure, (without filter)	8.100	14.300	17.450

In the first chart (I) the average leukocyte count (each curve representing the average of two dogs) following raying of the liver (*A*) splenic, (*B*) and intestinal, (*C*) areas for the various periods is shown. In these experiments the spleen dogs had a relatively high leukocyte count before the experiment was commenced. It will be observed that considerable differences in the type of response become manifest. The short sharp rise of the liver exposure is in contrast to the step-like effect of the intestinal exposure. Incidentally the latter reaches the maximum of reaction following the final exposure without filter. Raying of the splenic area evidently does not stimulate leukocytosis to any comparable degree. This corresponds in general with the observations previously recorded in the human and in experimental animals other than dogs.

The Differential Count. The differential count of the leukocytic response following the roentgen ray showed some variation, the chief difference being observed in a rather marked eosinophilia following the raying of the liver region. This effect is shown in the following table:

	Polymorphonuclear leukocytes. Per cent.	Small Mononuclears. Per cent.	Large mononuclears. Per cent.	Eosin. Per cent.
Normal	67	27	4	2.0
One-half hour after five minutes exposure of liver region	65	26	4	5.5
Five hours	77	15	3	4.5
Twenty-four hours	63	20	0	17.0
Forty-eight hours	62	21	6	11.0
Seventy-two hours	62	24	7	7.0

The eosinophilia reached its maximum after raying for 10-minute periods (average 11 per cent eosinophiles), but with the longer exposures was no longer so marked. It was observed in three of four dogs studied.

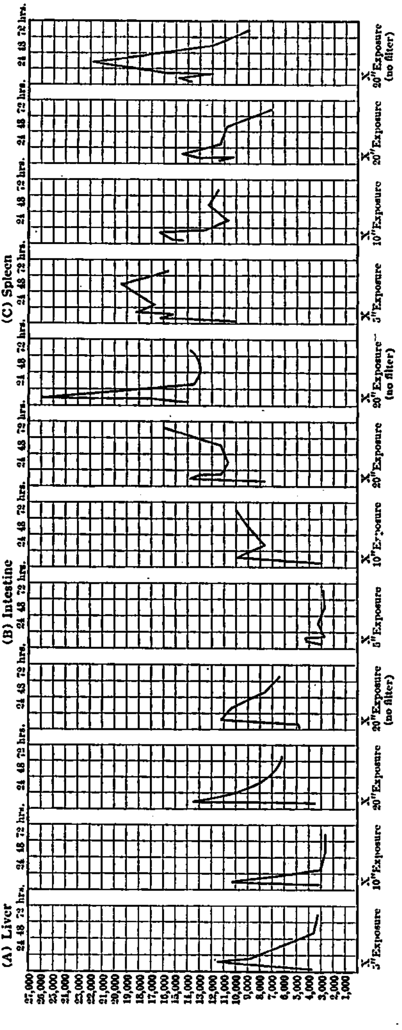
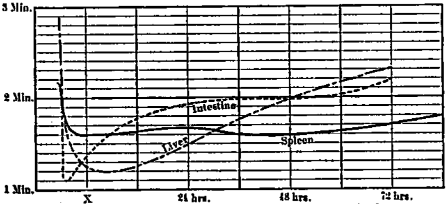


CHART I.—Effect of regional roentgenray exposure on the leukocyte curve.

Raying of the intestinal area and of the splenic area was followed by a fairly constant diminution of the mononuclear elements and a relative increase in the polymorphonuclear leukocytes. Nucleated red cells were occasionally observed in this group of animals; myelocytes seemed to occur more frequently in the blood after raying the liver, although a considerable number were observed after the more intense raying of the spleen.

Blood Coagulation. In studying the coagulation time we made use of capillary tubes drawn out to uniform caliber and the clotting time recorded when on breaking the tube a firm coagulum could be drawn out. A number of recent investigators, observing the reduction of the coagulation time following the raying of the splenic area have suggested that measure for therapeutic use in cases of hemorrhage. It is known that the raying of tumors and of lymphatic structures results in this effect on the coagulation. In our experiments the most prompt effect on the clotting time seemed to follow raying of the lower intestinal tract; the effect on the clotting time following raying of the splenic area was more delayed. In the latter case, however, the effect on the coagulation, especially after the longer raying periods, was more prolonged in effect.

In the following chart the average coagulation time is shown for the various periods:



The curves represent the averages for all the different periods of exposure.

CHART II.—Coagulation time of blood after raying liver, intestinal and splenic areas.

Nitrogen Excretion. Kjehldahl determinations were made in duplicate of the urine nitrogen excretion. Using the relatively moderate doses of roentgen rays indicated we were not able to determine an increase in the excretion of nitrogen as a result of the exposure except in the case of the liver area, where raying for the longest time periods (twenty minutes) resulted in an increase of the average excretion:

Average for three days before raying	1.3 gm.
Average for four days after exposure (including day of raying) .	2.1 "
Average for the next four days	1.7 "

Raying of the intestinal and splenic area had no such effect.

The non-coagulable nitrogen of the serum was never greatly altered, the only marked changes appearing in the serum after liver raying. The average NC nitrogen of the serum after ten minutes' raying was as follows (four animals):

	Normal, mg.	30 minutes after, mg.	1 hour after, mg.	5 hours after, mg.	24 hours, mg.
Liver area (per 100 cc) . .	21	23	31	30	29
After raying the intestinal area (three animals) (per 100 cc)	30	30	29	30	32
Splenic area (three animals) (per 100 cc)	17	18	17	17	17

With the longer periods of raying (twenty minutes with and without filter) the effects were even less apparent. Judging from Hall and Whipple's[23] results we may assume that we were dealing with relatively non-toxic doses, since in their animals which were given large and lethal doses the non-protein nitrogen of the serum was increased to a considerable degree.

Enzymes. *Protease.* Protease in the serum was determined by the chloroform method and the values represent the amount of nitrogen digest per cc in milligrams (twenty-four hours at 37° C.). It is apparent from a survey of the curves plotted in Chart III that differences in the extent of enzyme mobilization depended on the amount of roentgenray exposure as well as the area rayed.

The liver (III A) and intestine (III B) dogs had practically no protease present in the serum before raying and were not influenced by the smallest dose (five minutes). With exposure extended to ten minutes the intestine dogs responded by a prompt mobilization, the effect on the liver dogs being apparent as a somewhat delayed reaction, but persisting to the time of the next exposure. In this case exposure for twenty minutes again increased the amount of protease. A maximum effect for the liver exposure in these two dogs evidently lay between the ten and twenty-minute periods.

The spleen dogs (III C) differed to the extent that the initial serum titer tested before exposure contained a considerable amount of protease. (These two animals had an average leukocyte count of 10,000 as contrasted to the average of 3000 and 4000 for the intestine and liver animals.) Even the short roentgenray exposure resulted in a diminution of the titer, which, however, was recovered and even augmented before the second period of exposure. This second exposure (ten minutes) was followed by a slight increase and then a progressive diminution.

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[23] Am. Jour. Med. Sci., 1919, 157, 453.

Peptidase (Erepsin). The presence of a peptone-splitting enzyme in the serum has been reported at various times for several of the smaller laboratory animals as well as in the human. Our inability to secure glycyltryptophan compelled us to resort to Witte peptone, as reported in a previous paper (Petersen and Short[24]). The titer which we have used represents the minimum dilution of serum which in twenty-four hours' digestion still gives a definite tryptophan reaction with bromine water.

From a study of the curves (IV *a*, *b*, *c*) two distinct changes are apparent: First, that there is no correlation between the amount of proteolytic and peptolytic enzyme action in the serum. While in one increase a considerable amount of proteolysis may occur, there is no increase in the erepsin, or *vice versa*. On the other hand in periods when the one enzyme is increasing in titer the other enzyme may be diminishing its titer. (Charts III A and IV A.) Secondly, there is a decided difference in the response of ereptase with the raying of the different regions. The greatest and most persistent increase takes place following the raying of the gastro-intestinal tract. Raying of the splenic area seemed followed by least effect on the peptidase content.

Lipase. Serum lipase was titrated by the ethylbutyrate method and the charts represent the amount of free fatty acid liberated from 1 cc of ethyl butyrate by 1 cc of serum in twenty-four hours' incubation, and is expressed in terms of $\frac{N}{50}$ HCl. (Chart V, *A*, *B*, *C*)

Diastase (Amylase). Diastase in the serum was tested by the Wohlgemuth method, modifying the amount of the starch substrate (1 cc of 0.5 per cent solution of soluble potato starch), incubation being for twenty-four hours. It was found that the fluctuations of the diastase titer were very great, depending very probably on whether or not portions of the pancreas were included in the field of raying. The rôle of the pancreas, as well as other possible sources of blood amylase, has been discussed by King.[25] As a rule, raying of the liver area was followed by a greater mobilization of diastase than in the lower intestinal or splenic areas. In Chart VI the serum diastase expressed in Wohlgemuth units following a ten-minute exposure over the liver is illustrated.

Antiferment. Antiferment fluctuations following roentgen-ray stimulation were of considerable range, some of the exposures being followed by an increase and other by a decrease in the titer. In the table on page 118 (which shows the inhibition in percentage for the single serum unit, usually 0.025 cc serum, the antiferment alterations following raying of the splenic area are shown, together with the average.

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[24] Jour. Inf. Dis., 1918, **22**, 147.
[25] Am. Jour. Physiol., 1914, **35**, 301.

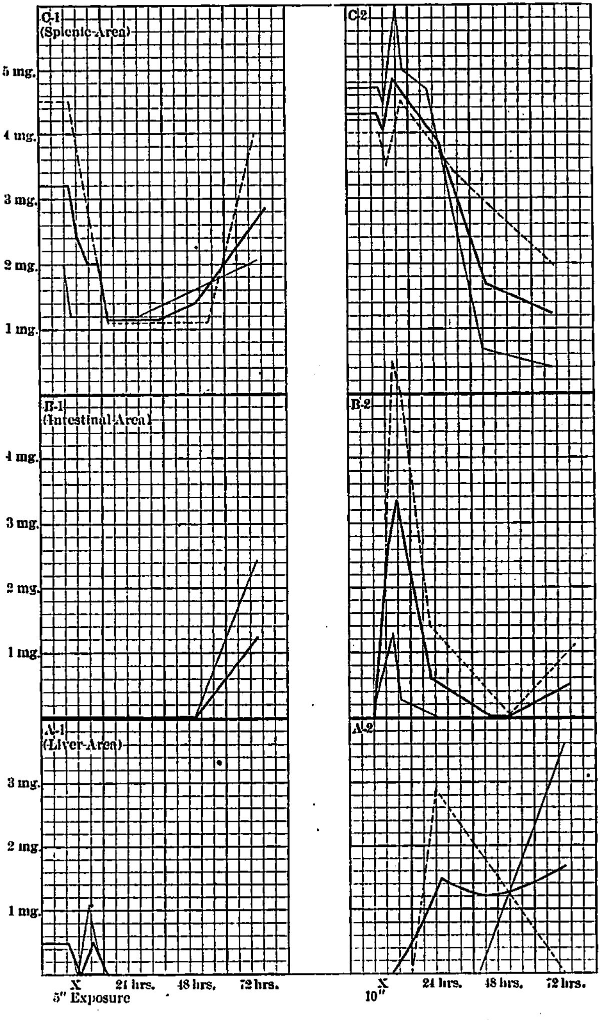
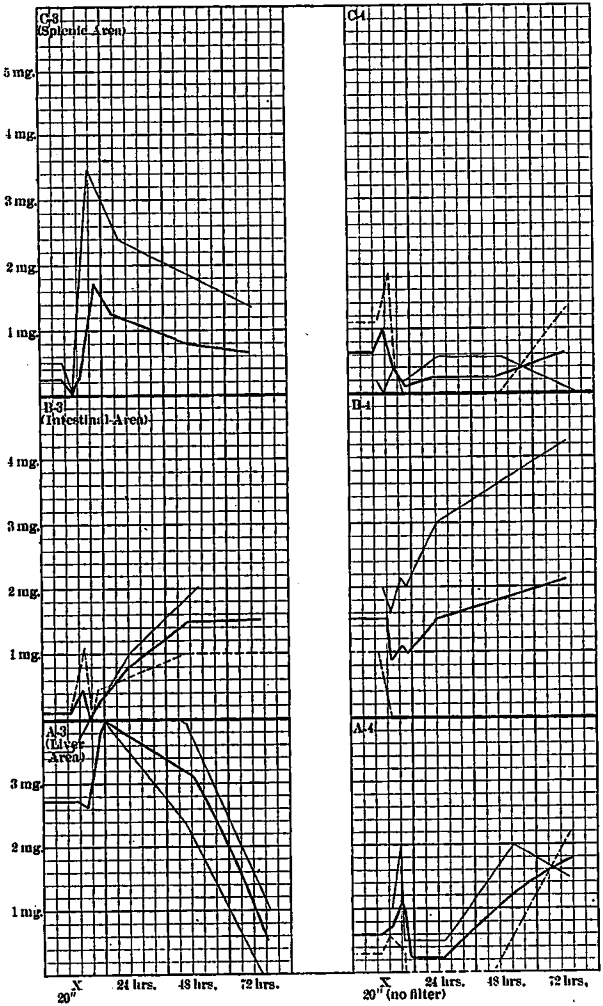


Chart III.—Mobilization of serum protease



following irradiation of various organs.

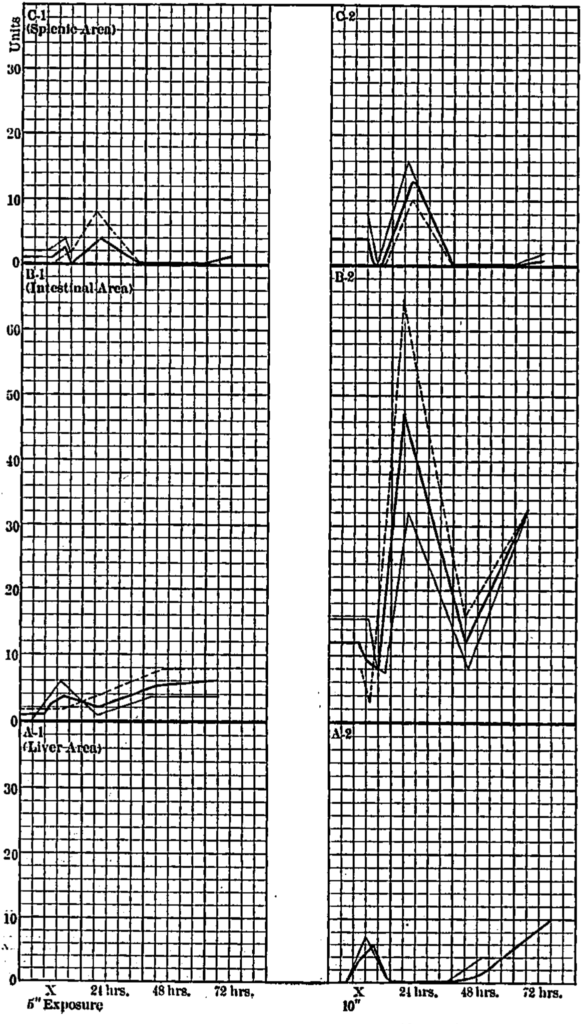
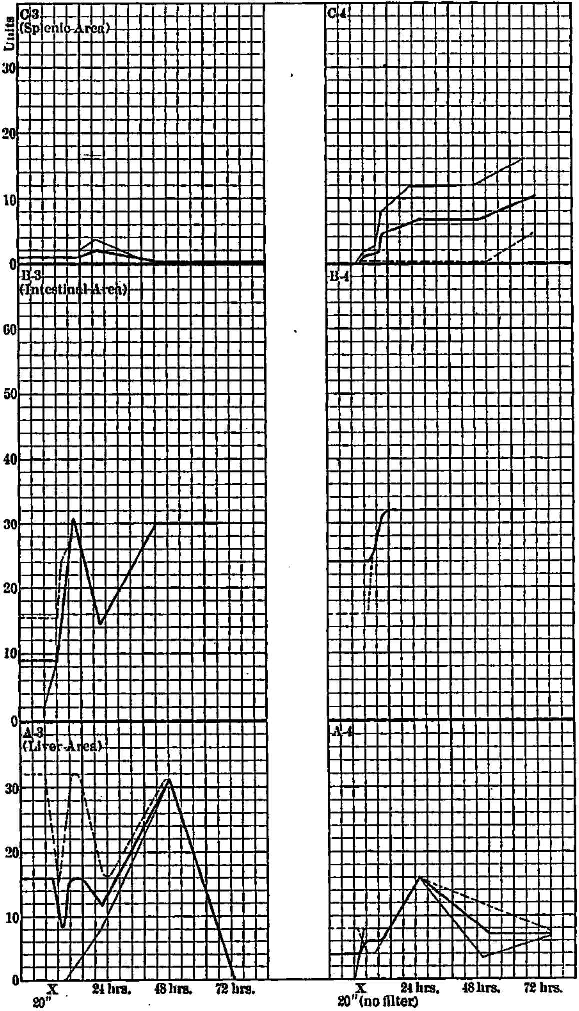


CHART IV.—Mobilization of serum



peptidase after regional irradiation.

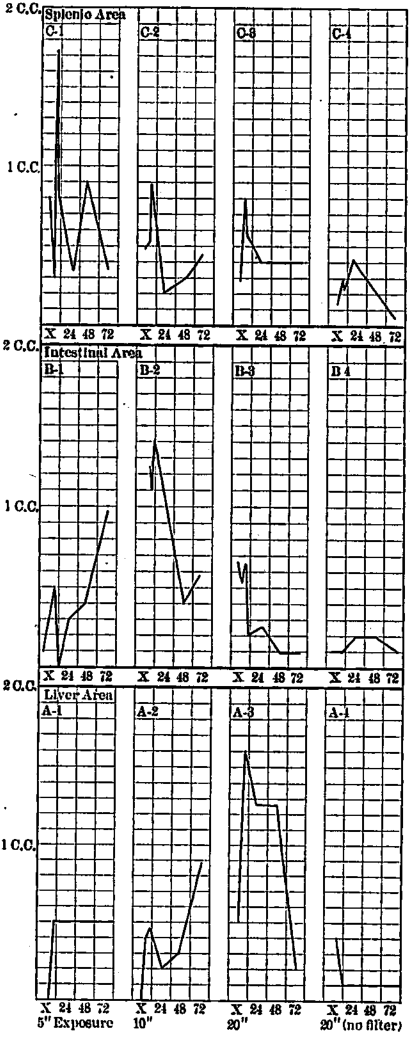


CHART V.—Lipase titer following regional roentgenray stimulation.

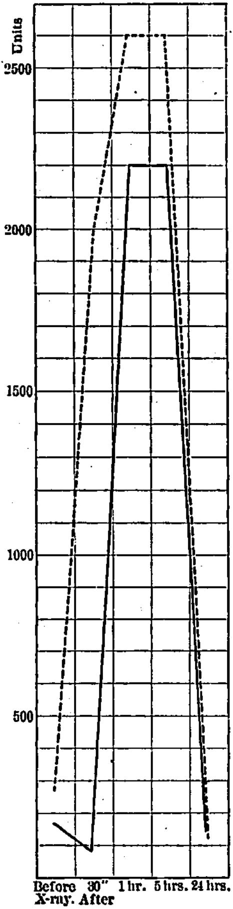


CHART VI.—Diastase titer following liver-raying (ten-minute exposure).

Before, per cent.	Minutes' exposure.	After 30 minutes, per cent.	1 hour, per cent.	5 hours, per cent.	24 hours, per cent.	48 hours, per cent.	72 hours, per cent.
0	10	50	0	50	20		
65	5	65	65	30	65	65	55
50	10	70	65	58	77	66	75
75	20	75	75	75	65	70	78
65	20	70	72	75	72	70	70
75	5	50	58	35	58	58	60
57	10	60	33	25	15	25	35
40	20	68	72	58	78	80	66
34	20	50	50	60	40	44	40
Average							
51		62	54	51	54	60	60

Discussion. The data presented in this paper seem to us to have a direct bearing on certain therapeutic applications of the roentgen ray and other related photodynamic and radiant agents, applications which heretofore seem to have been ignored because of the more obvious and direct uses of such agents in diagnosis or in local therapeusis. It is only in the relatively recent recognition of the value of heliotherapy in tuberculosis that we find evidence of this use of the indirect and systemic effect of a photodynamic agent.

Here the experience has been that such stimulation (heliotherapy) has a dual clinical effect in tuberculosis.[26] In the active case it is in general harmful because of an increased tendency to hemorrhage, augmentation of the temperature range, the amount of secretion, etc., all bearing evidence of an increase of focal activity of digestion of the connective tissue bulwark. In the quiescent case the clinical experience is, on the whole, favorable, the general resistance of the patient being apparently increased, the weight, the blood picture and subjective symptoms of the patient improved. This dualism in clinical effect we meet with in practically every agent used in the treatment of tuberculosis. We find it true of tuberculin. We find it true of the more recent non-specific methods: albumoses (Holler[27]), milk (Schmidt[28]), casein (Lindig[29]).

We are not yet familiar with the fundamental changes that underly heliotherapy or non-specific therapy, or specific tuberculin therapy for that matter. Very probable are the conclusions of Luithlen[30] and Starkenstein[31] and others that we have to deal primarily with changes in the permeability of the cells. According to this conception practically all the other recorded observations—changes in blood-forming organs, in clotting time, the fever and defervescence, the effect on the nervous system, on joints, liver and eye tissues, the increase in resorption of exudates, increase in muscular work and gland secretion, the increased resistance to intoxication—are merely the expressions in the various cell groups of such cell-membrane alterations. So, too, the enzyme mobilization which has been repeatedly suggested as the cause of the clinical improvement might be regarded as the result of the alteration in permeability.

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[26] Pottinger, F. M.: Interstate Med. Jour., 1915, **22**, 818.

[27] Beit. z. klin. der Infektionskr., 1917, **6**, 92.

[28] Deutsch. Arch. f. klin. Med., 1919, **131**, 1, and with Krauss, Deutsch. med. klin., 1919, **15**, 503.

[29] Arch. f. Gynäk., **110**, No. 3.

[30] Loc. cit.

[31] München. med. Wchnschr., 1919, **66**, 205.

With this in mind it seemed of some value to ascertain whether or not enzymes could be mobilized as a result of raying the abdominal organs, and if so, could qualitative differences be maintained by raying various organ complexes. The experiments here reported seem to bear out this assumption. Depending on the intensity of the roentgenray stimulation one can determine a maximum effect (which in our cases varied from ten to fifteen minutes' exposure), diminishing in either direction from a dose that was too small to cause appreciable differences (five minutes) to doses that were too large (twenty minutes to one hour). With these latter doses there was an actual diminution in the amount of serum enzymes titrated. Such a result is one that we might anticipate. Moderate doses will conceivably stimulate both cell activity in general and enzyme action itself, according to Richards's[32] experiments; larger doses would either leave that activity unaltered or result in an actual destruction of the enzymes.

In these experiments it is to be kept in mind that it is impossible to confine the roentgenray stimulation to any single organ. In raying the liver both the intestine and the pancreas would necessarily be included to some extent, as they would be, too, in raying the splenic area. In raying the intestinal area we endeavored to ray the lowest quadrant to avoid the simultaneous stimulation of other organs. It is also to be kept in mind that because of the duration of the periods of raying the blood and its elements must have passed through the rayed area many times. Some of the enzyme effect might have been derived from the leukocytes, which in the dog are relatively rich in proteolytic enzymes.

As previously stated, little attention has so far been paid to the possibility of organ stimulation by means of the roentgenray. Manoukhine[33] alone has carried out a series of experiments in tuberculosis. He rayed the spleen of tuberculous guinea-pigs and monkeys for varying periods and noted that such animals outlived his control animals for a considerable time, while animals in which the liver was rayed were unfavorably influenced. Manoukhine decided that when the spleen was rayed leukocytolysins were liberated, which, while destroying leukocytes, aided the organism in combating infection. When, on the other hand, the liver was rayed, leukocyte-protecting substances were formed and thrown into the circulation. Manoukhine treated a few human cases with encouraging results. Whatever the interpretation of the mechanism, these experiments bring the evidence that by means of selective organ stimulation therapeutic effects may be achieved.

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[32] Loc. cit.

[33] Wratsch Gazeta, 1914, 15, 617.

The spleen and its relation to resistance to tuberculosis has in recent years been studied extensively, more particularly in connection with mononuclear-cell reactions and the effect of extirpation and roentgenray exposure thereto. It might seem possible that along with the cellular reaction the serum alterations suggested in this paper resulting from roentgenray stimulation of selected organs may have a part in the phenomena of altered resistance to tuberculosis.

Conclusions. By means of selective organ stimulation by roentgen rays in moderate dosage it seems possible to influence the serum enzymes to a considerable degree. Such doses act in stimulating a mobilization of various enzymes; large doses lessen the titer of the serum enzymes.

Raying the hepatic area in dogs resulted in a temporary leukocytosis (with eosinophilia) as well as a well-defined increase in the titer of protease, peptidase, lipase and diastase in the serum.

Raying the intestinal area resulted in a more persistent leukocytosis and a marked mobilization of peptidase; the other enzymes were altered less in proportion.

Raying of the splenic area was followed in general by a diminution of the serum enzymes with the exception of the lipase.

Alteration in the coagulation time of the blood following raying was not confined to raying of the splenic area but followed exposure of the other regions as well. No alterations of complement titer were observed following organ stimulation. The antiferment was usually increased after periods of raying.

THE RELATION OF THE PITUITARY GLAND TO EPILEPSY.

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Since the publication of Cushing's memorable monograph on the hypophysis,[1] increasing interest has been directed to the possibility of an endocrine factor or factors as the causative agent of those convulsions which are classed under the broad term "epilepsy." With further knowledge of the functions of these glands the body of evidence as reflected in the literature has rested on the pituitary element as the predominating factor in the so-called "endocrine epilepsies," although some writers following the lead of Laignel-Lavastine[2] believe the thyroid is the glandular element at fault.

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[1] The Pituitary, 1911, W. B. Saunders Company, Philadelphia.

[2] The Internal Secretions and the Nervous System, 1919, Nervous and Mental Disease Publication Company.